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(54) Title: METHOD FOR TREATMENT OF DISORDERS OF ATTENTION

(57) **Abstract**

The present invention relates to the treatment of disorders of attention such as, for example, attention deficit disorder and Tourette's syndrome comprising administering to such a human or animal a safe and effective dose of an active compound selected from the group consisting of galanthamine, lycoramine, O–desmethylgalanthamine, lycoramine, O–desmethylgalanthamine, O–desmethyllycoramine or an ester, ether, carbamate or carbonate of one of these compounds or a pharmaceutically acceptable salt thereof.

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METHOD FOR TREATMENT OF DISORDERS OF ATTENTION

Field of the Invention

The present invention relates to the treatment of disorders of attention such as, for example, attention deficit disorder and Tourette's syndrome.

Cross Reference to Related Application

This application claims priority from U.S. Provisional Application 60/063,769 filed on October 29, 1997.

Background of the Invention

It has been known for a number of years that cholinergic stimulation of the brain causes increases in the state of awareness, for example as described in 1967 by Krnjevic in Anesthesiology Vol. 128 pp 100-104. However, attempts to use cholinomimetic or acetyl choline precursor compounds to treat attentional disorders in humans have had only limited success. Studies using nicotine have shown that it can have some benefit in treating attention deficit problems. Some improvement of attention has been noted in treatments with arecoline, a muscarinic agonist. However, this is a difficult drug to administer and has not been used outside studies.

In recent years a number of acetylcholinesterase inhibitors have been proposed for the treatment of Alzheimer's disease. In particular galanthamine has been proposed for the use in U.S. Patent 4,664,318 and many of its analogues and lycoramine analogues in PCT Publication WO 88/08708. However, as far as I am aware, there has been no suggestion that such compounds should be used for the treatment of disorders of attention. Compounds that have been suggested for use in the treatment for Alzheimer's disease include: aminoacridines such as tetrahydroaminoacridine (THA, also known as tacrine) and velnacrine, which are, however, bedeviled by toxicity problems which are likely to preclude their use in situations other than those where there is no alternative; physostigmine, which cause significant adverse peripheral effects that prevent it from being administered at a dosage level that would result in beneficial results in the brain and galanthamine and some of its analogs. Some reported studies of the use of tacrine in the treatment of Alzheimer's disease have shown some improvement in tasks involving attention in patients treated with tacrine, however, such results have been

inconsistent.

Summary of the Invention

According to the present invention there is provided a treatment for disorders of attention in humans or other animals which comprises administering to said human or animal a safe and effective dose of galanthamine, lycoramine, O-desmethylgalanthamine, O-desmethyllycoramine or an ester, ether, carbamate or carbonate of one of these compounds or a pharmaceutically acceptable salt of any of them.

Ester, ether, carbamate and carbonate groups may be bound to either the 2 or 13 position of the nucleus of the compound or to both of these positions.

Specific Description of the Preferred Embodiments

Galanthamine or lycoramine analogs of use in the present invention may be prepared by use of the methods described for example in PCT Publication WO 88/08708.

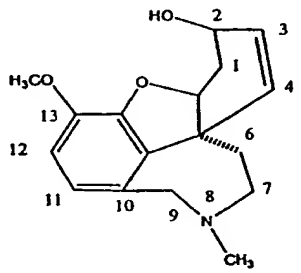
I have found that there is an improvement in the ability to carry out tasks requiring attention in patients treated with galanthamine at dosage levels in the range of 20 to 50 mg per day. The results obtained are significantly better and more consistent then those achieved using tacrine.

Suitable dosage rates for the present invention can be determined by standard techniques such as identifying potency based on animal studies, determining maximum tolerated dose are administered to subjects who are asked to complete certain standard attentional tasks such as the attentional question on the Mini-Mental State exam and the concentration/distractibility component of the Alzheimer's Disease Assessment Scale.

Suitable salts of galanthamine that may be employed in the treatment of the present invention include a variety of pharmaceutically acceptable salts including the hydrobromide and hydrochloride. Suitable esters include those of aliphatic carboxylic acids having from 2 to 6 carbon atoms and those of benzoic or substituted benzoic acids. Suitable carbamates include aliphatic carbamates such as mono and di alkyl carbamates of from 1 to 10 carbon atoms and aryl carbamates such as phenyl or naphthyl and substituted derivatives thereof. Suitable carbonates include aliphatic carbon such as alkyl carbon of from 1 to 10 carbon atoms in each

alkyl groups and aryl carbonates such as phenyl or naphthyl carbamates and substituted derivatives thereof. Suitable ethers include aliphatic ethers such as alkyl ethers of 1 to 6 carbon atoms, aromatic ethers such as phenyl and naphthyl and aryl ethers such as benzyl ethers. In the case of the O-desmethylgalanthamine and O-desmethyllycoramine, such ester, carbamate, carbonate, and ether groups may be bonded either to the 2 or the 13 position of the galanthamine or lycoramine core structure.

Different numbering systems have been used in the literature for galanthamine and lycoramine. The numbering system used in the present application is the following



In addition to galanthamine itself, its esters and carbonates and esters and carbonates of 13-desmethylgalanthamine such as the acetyl and other C_{1-6} alkanoyl esters of 13-desmethylgalanthamine are likely to be of particular use in the present invention. Other useful compounds include O-desmethylgalanthamine, galanthamine 2-methyl carbamate, galanthamine-2-n-butyl carbamate, galanthamine-2-α-naphthyl carbamate, galanthamine-13-n-butyl carbamate, and analogous lower alkyl (C_{1-8}) carbamates.

Compositions suitable for use in treatments according to the invention are typically suitable for oral administration such as tablets, capsules, or lozenges containing from 0.01 to 45 mg. of the active compound depending upon the cavity of the compound. In the case of galanthamine itself such dosage units typically comprise from 5 to 35 mg. of galanthamine or a pharmaceutically acceptable salt. For other compounds such as 13-desmethylgalanthamine-13-isopropyl carbonate and 13-desmethyl-13-pivaloate, dosages as low as about 0.5 mg. may be useful. If desired, such oral dosage forms may be sustained dosage formulations in which the particles of the active compound are coated so as to delay release into the blood

stream for example by coating with a pharmaceutically acceptable polymer that is dissolved in gastric juices such as polyvinyl pyrrolidone and then sizing the particles and incorporating specific ratios of particles of particular sizes into a tablet, capsule or lozenge so that particles having different degrees of thickness of coating are released at different times. In the present case, the coating technique will desirably result in most of the active compound being released within twelve hours of administration. Alternative means of application may include for example transdermal patches in which case the objective is to provide administration of a dosage at a rate of 0.001 to 10 mg., per hour.

The compounds for use according to the present invention share the same contraindications as other cholinergic drugs. Thus care should be taken before using the present invention on pre-pubertal children and patients who suffer for example from asthma, epilepsy, bradycardia, heart block, hemorrhagic ulcer disease. Furthermore, animal studies have shown that cholinergic drugs may result in overstimulation of the uterus and ovaries in premenopausal women.

CLAIMS

1. A method of treating disorders of attention in humans or other animals which comprises administering to such a human or animal a safe and effective dose of an active compound selected from the group consisting of galanthamine, lycoramine, O-desmethylgalanthamine, lycoramine, O-desmethyl-galanthamine, O-desmethyllycoramine or an ester, ether, carbamate or carbonate of one of these compounds or a pharmaceutically acceptable salt thereof.

2. A method as claimed in claim 1, wherein said active compound is used in the form of its hydrobromide or hydrochloride salt.

3. A method as claimed in claim 1 or claim 2, wherein the active compound is galanthamine.

4. A method as claimed in claim 1 or claim 2, wherein the active compound is O-desmethylgalanthamine.

5. A method as claimed in claim 1 or claim 2, wherein the active compound is selected from the 13-C_{1-6} alkanoyl esters, 13-benzoyl ester, 13-C_1-C_{10} mono or dialkyl carbamates, 13-phenyl carbamate, 13-α naphthyl carbamate, 13-C_1-C_{10} alkyl carbonates, 13-phenyl carbonate, 13-naphthyl carbonate, 13-C_2-C_6 alkyl ethers, 13-phenyl ether, 13-naphthyl ether and 13-benzyl ether of O-desmethyl-galanthamine.

6. A method as claimed in claim 1 or claim 2, wherein the active compound is selected from 2-C_{1-6} alkanyl esters, 2-benzoyl ester, 2-C_{1-10} mono or dialkyl carbamates, 2-phenyl carbamate, 2-α naphthyl carbamate, 2-C_{1-10} alkyl carbonates, 2-phenyl carbonate, 2-naphthyl carbonate of galanthamine.

7. A method as claimed in claim 1 or claim 2, wherein the active compound is a 2-C_{1-6} alkyl ether, 2-phenyl ether or 2-benzyl ether of galanthamine.

8. Use of a compound selected from galanthamine, lycoramine, O-desmethylgalanthamine, O-desmethyllycoramine or an ester, ether, carbamate or carbonate of one of these components or a pharmaceutically acceptable salt thereof for the treatment of attention deficit disorders.

9. A medicine comprising a compound selected from galanthamine, lycoramine, O-desmethylgalanthamine, O-desmethyllycoramine or an ester, ether, carbamate or carbonate of one of these components or a pharmaceutically acceptable

salt thereof for the treatment of attention deficit disorders.

10. Use of a compound selected from galanthamine, lycoramine, O-desmethylgalanthamine, O-desmethyllycoramine, or an ester, ether, carbamate or carbonate thereof or a pharmaceutically acceptable salt of any of these in the preparation of a medicament for the treatment of attention deficit disorders.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/22777

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 31/55
US CL : 514/215

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/215

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS ONLINE, DERWENT

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,155,226 A (LEE et al.) 13 October 1992, see the entire document.	1-10

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

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